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HEPATITIS C VIRUS INFECTION AND NON-HODGKIN LYMPHOMA: RESULTS OF THE NCI-SEER MULTI-CENTER CASE-CONTROL STUDY

Eric A. ENGELS[1]*, Nilanjan CHATTERJEE[1], James R. CERHAN[2], Scott DAVIS[3], Wendy COZEN[4], Richard K. SEVERSON[5], Denise WHITBY[6], Joanne S. COLT[1] and Patricia HARTGE[1]

[1]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services, Rockville, MD, USA*
[2]*Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA*
[3]*Fred Hutchinson Cancer Research Center, Seattle, WA, USA*
[4]*University of Southern California, Los Angeles, CA, USA*
[5]*Karmanos Cancer Institute and Department of Family Medicine, Wayne State University, Detroit, MI, USA*
[6]*Viral Epidemiology Section, AIDS Vaccine Program, National Cancer Institute-Frederick, Frederick, MD, USA*

Several studies have noted elevated hepatitis C virus (HCV) prevalence among patients with non-Hodgkin lymphoma (NHL), suggesting that HCV infection increases NHL risk through chronic immune stimulation. Population-based data from the U.S. are lacking. In a population-based case-control study of NHL in the United States, we identified HCV infection using an enzyme immunoassay, confirmed by recombinant immunoblot assay or HCV RNA detection. The association between HCV and NHL was assessed using logistic regression, adjusting for demographic factors, illicit drug use or medical history. Thirty-two of 813 (3.9%) NHL cases and 14 of 684 (2.1%) controls were HCV-infected [odds ratio (OR) 1.96, 95%CI 1.07–4.03]. For separate NHL subtypes, numbers were limited. Nonetheless, positive associations were noted for follicular (OR 2.46, 95%CI 1.01–5.81), marginal zone (3.99, 0–13.6) and mucosa-associated lymphoid tissue (2.04, 0–7.20) NHLs. For all NHLs combined, the HCV-NHL association changed little after adjustment for sex, age, race and study center (OR 1.89, 95%CI 1.00–4.00). HCV was common in controls who had injected drugs (40%) or used other illicit drugs (6.5%), but adjustment for drug use did not affect the HCV-NHL association (OR 1.87, 95%CI 0.95–4.10). Transfusion history was unrelated to HCV status, and adjustment for this exposure did not attenuate the HCV-NHL association (OR 2.15, 95%CI 1.12–4.76). Excluding 4 subjects with a history of hemodialysis or 3 subjects with organ transplants also did not affect the results. Our study demonstrates an association between HCV infection and NHL in the United States. HCV infection may be a cause of NHL.

Key words: *hepatitis C virus; non-Hodgkin's lymphoma; case-control study*

Hepatitis C virus (HCV) has been suggested to be a cause of non-Hodgkin lymphoma (NHL), but the evidence to date is conflicting. HCV infection is readily acquired through exposure to contaminated blood and frequently leads to chronic hepatitis and viremia.[1] Chronic HCV infection might plausibly cause NHL by inducing chronic B lymphocyte proliferation through persistent antigenic stimulation.[2,3]

Several epidemiological studies, mostly in Italy, have noted increased HCV prevalence in patients with NHL (*i.e.*, 9–37% in NHL cases *vs.* 3–10% in control groups).[4–9] Other studies in North America and Europe have failed to confirm the association.[10–13] To some extent, varying results across geographic regions may reflect the low statistical power of some studies to detect an association because HCV infection is relatively uncommon in North America and much of Europe (*i.e.*, approximately 2% prevalence). Importantly, some prior studies compared HCV prevalence in NHL cases with HCV prevalence in individuals with other medical conditions or with results from general surveys, which could have led to bias. Also, because HCV is often acquired through blood transfusion or injection drug use,[14] the possibility exists that the association between HCV and NHL is mediated by exposure to blood itself or other agents conveyed by blood, but this has not been systematically examined. Finally, although most studies have suggested an association primarily with low- or intermediate-grade NHL, at least 1 study found elevated HCV prevalence in a wide range of lymphoproliferative disorders,[15] calling into question the specificity of the association.

In this report, we present the results of a large U.S. population-based case-control study of the association between HCV and NHL. In the U.S., HCV prevalence is estimated to be 2% in the general adult population.[16] Thus, our study helps to characterize the HCV-NHL association in a population with a low prevalence of HCV. Secondary objectives were to examine further the range of NHL subtypes associated with HCV infection and assess whether the HCV-NHL association was independent of reported histories of injection drug use, blood transfusion and medical procedures (i.e., hemodialysis and organ transplantation) associated with blood exposure or NHL.

METHODS

Study description

The study population comprised 4 areas covered by the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI): the state of Iowa, and the metropolitan areas of Detroit, Los Angeles and Seattle. Eligible cases were sampled from individuals 20–74 years old, prospectively identified with incident (*i.e.*, newly diagnosed) NHL between July 1998 and June 2000 (N=2,248). In Detroit and Los Angeles, African-American cases were over-sampled. Eligible controls (N=2,409) were selected from the general population in the 4 areas, stratified on residence, age sex, and race, to parallel the distribution in the cases; controls were identified using random digit dialing (subjects aged 20–64 years) or from Medicare eligibility files (subjects aged 65–74 years). Individuals who were identified by themselves or their physicians as HIV-infected were excluded from the study.

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*Correspondence to: Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, DHHS, 6120 Executive Boulevard, EPS 8010, Rockville, MD 20892, USA.
Fax: +301-402-0817. E-mail: engelse@exchange.nih.gov

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From the eligible pool, 2,378 individuals (1,321 cases and 1,057 controls) were interviewed and included as study subjects (320 eligible NHL cases were deceased when contact was attempted, while the most common other reason for nonparticipation was physician or subject refusal). Trained interviewers administered a computer-assisted interview in the home, which covered a wide variety of topics, such as residential history and pesticide use, education and occupational history and medical history, including history of blood transfusion, hemodialysis or receipt of organ transplant. Because of the length and complexity of the interview questionnaire, by design some questionnaire components, including questions on illicit drug use, were administered to only half of the study subjects. Medical records were not reviewed.

Data on NHL pathologic types were derived from each local SEER registry and were based on abstracted reports of the diagnosing pathologist. Histologic diagnoses were coded using the International Classification of Diseases for Oncology (second ed.),[17] which was updated to include categories in the Revised European-American Lymphoma classification.[18]

Subjects were asked to provide a blood sample, which was shipped to a central repository for processing and storage. We evaluated HCV status on all 1,497 subjects who had available blood samples, including 813 cases (61.5% of all cases) and 684 controls (64.7% of all controls). Subjects tested for HCV were similar to those not tested in terms of sex (53.8% *vs*. 51.2% male, $p=0.21$) but were slightly older (mean age at diagnosis or selection 57.6 *vs*. 56.5 years, $p=0.05$) and were more likely to be white (87.4% *vs*. 74.6%, $p<0.0001$) and to be from Iowa or Seattle (67.1% *vs*. 28.2%, $p<0.0001$).

In the study consent procedure, subjects were informed that their blood samples would be used to study NHL-associated environmental exposures. However, subjects did not specifically consent to be tested for viral infections, including HCV. Therefore, we anonymized specimens prior to performing HCV tests. Laboratory testing for HIV was explicitly excluded in the study protocol.

Laboratory methods

Sera were screened for HCV antibodies using a third generation enzyme immunoassay (Ortho, Raritan, NJ) with 97–99% sensitivity and >99% specificity.[19] Positive samples were tested further for serum HCV antibodies using a third generation recombinant immunoblot assay (RIBA, Ortho) and for serum HCV RNA (Amplicor, version 2.0, Roche Diagnostics, Indianapolis, IN). Samples were considered HCV-positive if the RIBA or Amplicor results were positive. Among cases, HCV testing was performed a median of 21 weeks after NHL diagnosis (interquartile range 15–36 weeks).

Statistical methods

In the primary analysis, we compared HCV prevalence in cases and controls. In secondary analyses, we examined HCV prevalence for NHL subtypes defined by the World Health Organization,[20] groupings of these NHL subtypes by Working Formulation grade,[17] and NHL site (nodal, extranodal). In adjusted analyses, we used logistic regression to measure the independent association between HCV and NHL. Specifically, we adjusted for demographic factors (sex, age, race, center and education) or for histories of drug use and blood transfusion. Because HCV is commonly acquired through injection drug use,[14] we considered categories of illicit drug use as any injection drug use, other illicit drug use and no illicit drug use. Since only half of subjects were administered a questionnaire on drug use, we considered individuals with no ascertained history as a fourth category. We categorized transfusion histories as transfused before 1990 (the year that HCV screening of blood donors was introduced in the U.S.), transfused in 1990 or after and never transfused; the minority of subjects with missing data on transfusion history were excluded from these analyses. In other analyses, we excluded the minority of subjects with a history of hemodialysis or receipt of an organ transplant, since these medical conditions are associated with elevated HCV prevalence.[14,21]

Owing to small numbers of HCV-infected cases and controls, we did not rely on standard asymptotic methods for obtaining confidence intervals and *p*-values. Instead, we used resampling-based methods, specifically the bootstrap for confidence intervals and permutation tests for hypothesis testing.[22,23] Statistical calculations were performed in S-Plus 2000 (Mathsoft, Seattle, WA) and MATLAB (MathWorks, v5.3.0.29215a-R11, Natick, MA).

RESULTS

Demographic characteristics of cases and controls tested for HCV infection are presented in Table I. Cases and controls were similar in terms of sex, age, study center and education. Cases and controls differed by race ($p=0.02$), with controls more likely than cases to be African American (8.5% *vs*. 5.2%).

Overall, 54 subjects (3.6%) were reactive on the screening HCV enzyme immunoassay, of whom 46 (85%) had confirmatory evidence of infection: HCV infection was confirmed for 38 subjects by RIBA, for 45 subjects by Amplicor and for 37 subjects by both RIBA and Amplicor. Thus, 45 of 46 HCV-infected subjects (98%) had HCV viremia, as documented by the Amplicor assay. Of the 46 subjects with confirmed HCV infection, 32 were cases (HCV prevalence in cases, 3.9%) and 14 were controls (HCV prevalence in controls, 2.1%). Because only 1 HCV-infected subject did not have HCV viremia, we could not examine whether the prevalence of viremia differed in cases and controls.

Among controls, HCV prevalence tended to be higher in males than females (3.0% *vs*. 1.0%, $p = 0.06$). HCV prevalence differed across race ($p=0.03$), being lower in whites (1.7%) and African Americans (1.7%) than persons of other race (8.6%). HCV prevalence was unrelated to age or education ($p_{trend} = 0.64$ and 0.31, respectively). HCV prevalence was 2.8% in Los Angeles, 3.1% in Seattle, 1.3% in Detroit and 0.9% in Iowa ($p = 0.48$). Among HCV-infected subjects with data on risk factors, 8 of 26 (31%) reported previous injection drug use and 13 of 45 (29%) reported receiving a blood transfusion before 1990. Among the 25 HCV-

TABLE I – STUDY SUBJECTS[1]

Category	Cases ($N = 813$)	Controls ($N = 684$)	*p*-value*
Sex			0.78
Male	435 (53.5)	371 (54.2)	
Female	378 (46.5)	313 (45.8)	
Age at diagnosis or selection, years			0.06
20–34	41 (5.0)	40 (5.9)	
35–44	103 (12.7)	64 (9.4)	
45–54	169 (20.8)	129 (18.9)	
55–64	221 (27.2)	157 (23.0)	
65–74	279 (34.3)	294 (43.0)	
Mean age (standard deviation)	57.0 (12.3)	58.2 (12.4)	
Race			0.02
White	718 (88.3)	591 (86.4)	
African American	42 (5.2)	58 (8.5)	
Other	53 (6.5)	35 (5.1)	
Center			0.81
Detroit	88 (10.8)	77 (11.3)	
Iowa	287 (35.3)	235 (34.4)	
Los Angeles	183 (22.5)	144 (21.1)	
Seattle	255 (31.4)	228 (33.3)	
Education, years			0.23
0–11	72 (8.9)	61 (8.9)	
12–15	521 (64.1)	413 (60.4)	
16 or more	220 (27.1)	210 (30.7)	

[1]Values in table for cases and controls are number (%), except where stated.–**p*-values were computed using the chi-square test, except for age (2-sample *t*-test) and education (Mantel Haenszel chi-square test for trend).

infected subjects with data on both injection drug use and transfusion, 12 (48%) reported neither risk factor. No HCV-infected subject reported a history of hemodialysis or receipt of organ transplant.

HCV infection was significantly associated with NHL overall [unadjusted odds ratio (OR) 1.96, 95%CI 1.07–4.03]. When we considered NHL subtypes separately, the number of subjects was small in most instances (Table II). Nonetheless, ORs were greater than 2.00 for 3 histologic subtypes in which the number of HCV-infected cases was at least 2: follicular (OR 2.46, 95%CI 1.01–5.81), marginal zone (OR 3.99, 0–13.6) and mucosa-associated lymphoid tissue (MALT) NHL (OR 2.04, 0–7.20). Similarly, an association was apparent for low-grade B-cell NHLs overall (OR 2.19, 95%CI 0.96–4.61). Based on 2 or more HCV-positive cases, associations were also suggested for T-cell NHL overall (OR 1.99, 95%CI 0–6.52) and NHL with other/unknown histology (OR 2.62, CI 0.49–7.14; Table II). Overall, the differences in ORs across NHL subtypes were not significant ($p=0.91$). Associations with HCV were seen for both nodal and extranodal NHLs (unadjusted ORs 2.03, 95%CI 1.06–4.28, and 1.82, 0.69–4.23, respectively; Table II).

For all NHLs combined, the association between HCV and NHL remained apparent after adjustment for sex, age, race and center (adjusted OR 1.89, 95%CI 1.00–4.00). Further adjustment for education did not affect this association (adjusted OR 1.84, 95%CI 1.01–4.14). Adjusted analyses could not be performed for NHL subtypes due to small numbers of HCV-infected subjects.

Information on illicit drug use was available on 792 subjects (53%). Among controls, HCV prevalence was highest in those who had used injection drugs (2 of 5 subjects HCV-positive, 40%), intermediate among those who had used other illicit drugs (3/46, 6.5%) and lowest among others (3/306, 1.0%, $p=0.007$). Nonetheless, after adjustment for drug use history, HCV infection remained associated with NHL risk (adjusted OR 1.87, 95%CI 0.95–4.10).

Information on transfusion history was available on 1,479 subjects (99%). Among controls, HCV infection was actually less common in those who had received a transfusion before 1990 (1 of 82 subjects HCV-positive, 1.2%) or received a transfusion in 1990 or after (0/34, 0%) than in those who were never transfused (12/546, 2.2%). Also, NHL was not associated with either blood transfusion before 1990 (OR 0.94, 95%CI 0.69–1.31) or blood transfusion in 1990 or after (0.95, 95%CI 0.59–1.57). Finally, after adjustment for transfusion history, the association between HCV and NHL was slightly stronger (adjusted OR 2.15, 95%CI 1.12–4.76).

Only 4 subjects had a prior history of hemodialysis and 3 had a history of receipt of an organ transplant (2 of these subjects had a history of both hemodialysis and organ transplant). As mentioned above, none of these individuals was HCV-infected. The association between HCV and NHL was unchanged by excluding the few subjects with a history of hemodialysis, organ transplant or either condition (data not shown).

DISCUSSION

In our study, we estimated that HCV-infected individuals have a 2-fold risk for NHL, compared to the general population. The observed association between HCV and NHL persisted after adjustments for demographic factors, drug use or history of blood transfusion, hemodialysis or organ transplant. Positive associations were noted for 3 low-grade NHL subtypes (follicular, marginal zone and MALT NHLs) and for both nodal and extranodal NHLs. For specific subtypes with small numbers of cases, we could not reliably assess the association with HCV.

An important strength of our study is its use of population-based sampling of NHL cases and controls. This allowed us to directly compare HCV prevalence in incident NHL cases with that in the general population. With this design, calculated ORs can be interpreted as a straightforward measure of relative risk.[24] Although not all eligible individuals participated in the study and not all subjects provided blood samples for testing, HCV prevalence in our controls overall and in demographic subgroups closely mirrored nationwide estimates,[16] supporting our approach. Another strength was our study's size, which allowed us to estimate the overall effect with precision, despite the low background prevalence of HCV infection in the U.S.[16] Finally, our study included data on NHL histology and site, allowing us to investigate specific subtypes, and on HCV risk factors.

TABLE II – ASSOCIATIONS BETWEEN HEPATITIS C VIRUS INFECTION AND NON-HODGKIN LYMPHOMA[1]

Category	N	HCV-positive, *n* (%)	Unadjusted OR (95% CI)
Controls	684	14 (2.1)	1.00
Cases, all NHL subtypes	813	32 (3.9)	1.96 (1.07–4.03)
Cases, by histologic subtype and grade			
Low-grade B-cell NHL	411	18 (4.4)	2.19 (0.96–4.61)
SLL/CLL	91	2 (2.2)	1.08 (0–3.45)
Lymphoplasmacytoid	20	1 (5.0)	2.52 (0–10.8)
Follicular	225	11 (4.9)	2.46 (1.01–5.81)
Marginal zone	26	2 (7.7)	3.99 (0–13.6)
MALT	49	2 (4.1)	2.04 (0–7.20)
Intermediate-and high-grade B-cell NHL	275	8 (2.9)	1.43 (0.49–3.19)
Mantle zone	37	1 (2.7)	1.33 (0–5.87)
DLBCL	217	6 (2.8)	1.36 (0.39–3.27)
DLBCL, immunoblastic variant	13	0	0 (—)
Burkitt	8	1 (12.5)	6.84 (0–36.6)
T-cell NHL	50	2 (4.0)	1.99 (0–6.52)
Mycosis fungoides	14	1 (7.1)	3.68 (0–17.8)
Other T cell	36	1 (2.8)	1.37 (0–5.66)
Other/unknown[2]	77	4 (5.2)	2.62 (0.49–7.14)
Cases, by primary site			
Nodal	540	22 (4.1)	2.03 (1.06–4.28)
Extranodal	273	10 (3.7)	1.82 (0.69–4.23)

[1]HCV, hepatitis C virus; NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; MALT, mucosa-associated lymphoid tissue; DLBCL diffuse large B cell lymphoma.–[2]"Other/unknown" NHL subtypes include cases where histology was not provided or was listed as "not otherwise specified" (61 cases), diffuse NHL (International Classification of Diseases for Oncology morphology code 9595, 3 cases), diffuse small cleaved cell NHL (code 9672, 9 cases) or diffuse small noncleaved cell NHL (code 9686, 4 cases).

One potential limitation of our study was the assessment of HCV infection status after NHL diagnosis, but this is unlikely to have distorted the relative risk estimates. NHL patients may receive transfusions during treatment, but only transfusions prior to 1990 conveyed appreciable risk for HCV transmission, while our cases were enrolled beginning in 1998. We confirmed HCV infections in almost all individuals with an assay demonstrating circulating virus, so false-positive HCV antibody results among NHL cases could not explain our findings. If anything, we might have underestimated HCV prevalence among cases, if immunocompromized NHL patients failed to mount a detectable antibody response to HCV infection.

The current finding of an overall increased HCV prevalence in persons with NHL is generally consistent with, though less marked than, results from previous studies in the U.S. and Italy. Specifically, hospital-based studies from Italy described 9–37% HCV prevalence among NHL patients, well above that seen in patients with other medical conditions or in serosurveys of the general Italian population (4–7) As in our study, the relationship with HCV infection in some Italian studies was apparent for low-grade subtypes (such as small lymphocytic, lymphoplasmacytoid and marginal zone NHLs), with ORs of 4–13,[4–7] although the most recent study also found associations for higher grade NHLs.[9] In a study in Los Angeles, Zuckerman *et al.*[8] found HCV infection in 22% of individuals with NHL and only 5% of controls with other medical conditions (OR 5.4). HCV infection was especially common (46% prevalence) among cases who had "monocytoid B-cell lymphoma," now classified under the World Health Organization scheme as marginal zone lymphoma.

On the other hand, similar studies based in France and Canada failed to confirm these associations.[10–12] Also, Rabkin *et al.*[13] recently described negative results from a case-control study nested within a large cohort followed in California. The Rabkin study evaluated HCV infection status using sera collected prospectively, on average 2 decades before NHL diagnosis. Of 57 B-cell NHL cases, none had prior evidence of HCV infection. Importantly, that study would not have detected an association with HCV if infection had occurred closer to the onset of NHL, *i.e.*, if the latency period between infection and NHL were short. Also, because of the prevalence of HCV in these countries, the negative studies had rather low power to detect an association between HCV and NHL.[10–13]

Several lines of biological evidence point to HCV as a cause of NHL. HCV infection is nearly universally present in essential mixed cryoglobulinemia,[25,26] a low-grade lymphoproliferative disorder that can evolve into NHL. Furthermore, HCV-infected individuals frequently harbor circulating B lymphocytes with chromosomal translocations involving the *bcl2* oncogene.[27] Persistently detectable *bcl2* translocations are associated with a high risk for progression to frank NHL,[28] and successful treatment of HCV infection results in loss of these translocations.[28] Although HCV can establish persistent infection of B lymphocytes,[29] HCV does not integrate into the host genome and does not possess oncogenes. Thus, the mechanism for HCV-mediated lymphomagenesis may likely involve chronic B lymphocyte stimulation through specific immune-related interactions. Along these lines, immunoglobulins produced by NHLs in some cases recognize the HCV E2 envelope protein.[2,3] Also, HCV binds to CD81 on the surface of B lymphocytes,[30] which might facilitate B lymphocyte activation. Finally, in HCV-infected patients with splenic marginal zone lymphoma, interferon-α-based therapy leads to resolution of HCV viremia and, concurrently, complete regression of the NHL.[31] The coincident clearance of HCV and clinical remission of NHL provides strong evidence that HCV plays a continuing role even in fully developed NHL. Of interest, NHL patients with virologic and hematologic responses to interferon-α still have detectable NHL-associated molecular rearrangements in circulating lymphocytes,[31] indicating that some steps in lymphomagenesis are not reversible with clearance of HCV.

If HCV infection increases NHL risk, as the current data and other evidence suggest, it is not clear whether all NHL subtypes are equally affected. Although most commonly demonstrated for a variety of low-grade NHL subtypes, associations with HCV infection have been noted for intermediate- and high-grade subtypes as well.[4,5,7,9] In our study, the magnitude of association with HCV infection did not differ significantly across histological subtypes or sites (nodal *vs*. extranodal), but we lacked the study size needed to discern associations with less common NHL subtypes or to rule out a general effect of HCV on NHL risk.

We considered the possibility that HCV infection is a marker for another blood-related exposure that is itself associated with NHL. HCV was present in blood transfusions given before 1990,[32] and transfusions have been linked with increased NHL risk.[33] Nonetheless, in the present study, HCV infection was not especially common in persons reporting pre-1990 receipt of blood, and prior transfusion was not associated with increased NHL risk. Similarly, our finding of an association between HCV and NHL was not due to HCV infections in individuals with a history of hemodialysis or organ transplant, since these conditions were rare.

HIV, which strongly increases NHL risk, could conceivably have been present in some of our HCV-infected subjects. Both HIV and HCV infections are common among injection drug users. However, our study had few injection drug users, and we excluded all individuals known to be HIV-infected. Additionally, drug use was not itself significantly associated with NHL, and adjustment for drug use did not attenuate the observed association between HCV and NHL. Furthermore, HIV increases risk most strongly for intermediate- and high-grade NHL subtypes,[34] whereas we most clearly identified associations between HCV and low-grade NHLs. HCV infection was absent in all 8 subjects with central nervous system lymphoma, a type prominently linked with HIV. Finally, prior studies identified an association between HCV and NHL among individuals known to be HIV-uninfected.[7,8] Thus, undiagnosed HCV-HIV co-infection is an unlikely explanation for our findings.

In conclusion, our study identifies an association between HCV infection and NHL in the U.S. Chronic HCV infection may predispose to a broad range of NHL subtypes through prolonged stimulation of B cell proliferation. Additional studies are needed to confirm these results, further characterize the spectrum of HCV-related NHLs and identify possible mechanisms responsible for HCV-related lymphomagenesis.

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